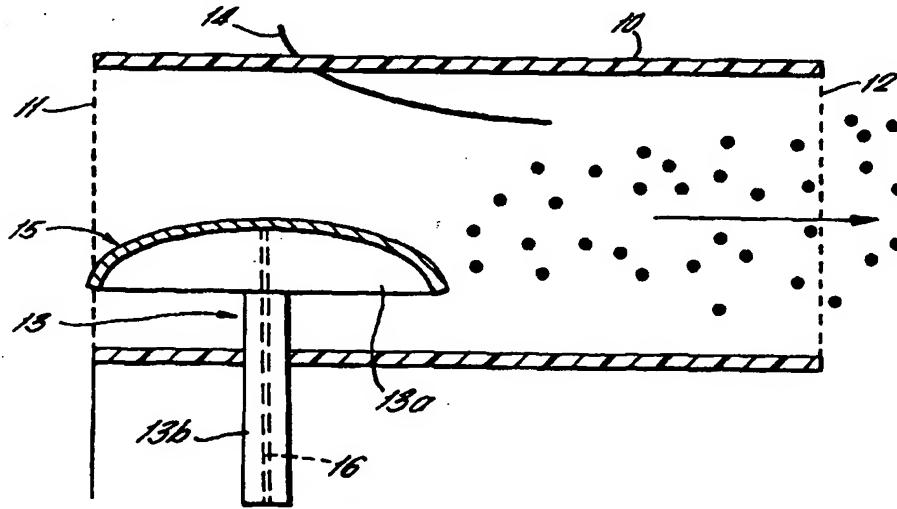




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : <b>A61M 15/00, B05B 5/025</b>		A1	(11) International Publication Number: <b>WO 99/42153</b>
			(43) International Publication Date: <b>26 August 1999 (26.08.99)</b>
(21) International Application Number: <b>PCT/GB98/03415</b>			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: <b>13 November 1998 (13.11.98)</b>			
(30) Priority Data: <b>9803643.7 20 February 1998 (20.02.98) GB</b>			
(71) Applicant (for all designated States except US): BESPAK PLC [GB/GB]; Bergen Way, North Lynn Industrial Estate, King's Lynn, Norfolk PE30 2JJ (GB).			
(72) Inventors; and			Published
(75) Inventors/Applicants (for US only): BARNES, Paul [GB/GB]; 15 Graham Drive, Fair Green, Middleton, King's Lynn, Norfolk PE32 1RL (GB). BALACHANDRAN, Wamadeva [GB/GB]; 9 Beechcroft Drive, Guildford, Surrey GU2 5SA (GB). MACHOWSKI, Wojciech [GB/GB]; 17 Merrow Court, Guildford, Surrey GU1 2SA (GB).			With international search report.
(74) Agent: BOULT WADE TENNANT; 27 Furnival Street, London EC4A 1PQ (GB).			

## (54) Title: INHALATION APPARATUS



## (57) Abstract

This invention relates to inhalation apparatus for dispensing an inhalable substance and, in particular, but not exclusively, to apparatus for use in the delivery of therapeutic substances to the human lung. There is provided apparatus for dispensing an aerosol of electrostatically charged droplets comprising a housing having an open ended duct (10) in which are located a first electrode (13) having an upper surface (15) lying in a generally longitudinal plane of the duct and a second electrode spaced from the first electrode. The apparatus further comprises means for delivering a metered quantity of liquid to the upper surface (15) of the first electrode for atomisation, and charging means for applying a higher potential to the second electrode with respect to the first electrode to effect atomisation.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INHALATION APPARATUS

This invention relates to inhalation apparatus for dispensing an inhalable substance and in particular, but not exclusively, to apparatus for use in the delivery of therapeutic substances to the human lung.

Medicinal inhalers are well known and have made a significant contribution to ailments such as asthma. Of particular usefulness are hand-held metered dose inhalers and dry power inhalers. Each produces an aerosol of fine particles containing medicament and which are carried into the respiratory system as a user inhales.

Several factors are known to effect the site at which deposition of such airborne particles are deposited in the respiratory system. Research has revealed that the electrostatic charge on the particles plays a very important part in determining the site of deposition and it has been shown that the level of electrostatic charge can be used to control particularly the site of deposition. A site may thereby be selected which is higher or lower in the bronchial tree to meet requirements of a particular therapeutic or diagnostic procedure. The level of charge can also serve to reduce the amount of particles lost through exhalation and this is particularly important where small quantities of medicament are delivered.

One means of achieving this is found in WO-A-94/19042 which describes dispensing apparatus for discharging a metered dose of a liquid in aerosol form from a pressurised dispensing container. The droplets are propelled through a passageway towards an inhalation port passing through a charging region.

The charging region contains one electrode which has at least one pointed feature and a second electrode having cooperating features of relatively low curvature. The aerosol emerging from the apparatus 5 will carry an inherent level of electrostatic charge. The charge can be modified in a controlled manner by imparting further electrostatic charges to the particles as they pass through the charging region before being inhaled.

10 For certain applications it is desired to use electrostatic forces for generating an aerosol of electrically charged droplets particularly of a much smaller amount of liquid such as a single drop, which the above described apparatus would be unable to 15 achieve.

EP-A-0224352 describes a method of generating a charged spray for ocular treatment. The formulation is supplied to a hollow spray nozzle which has an opening of such small cross-section as to retain up to 20  $\mu$ l of the formulation by surface tension. A metered dose of the formulation is supplied to the nozzle, after which a piston is activated to provide a current of air to force the formulation out of the nozzle. At the same time a high voltage is applied to a region of 25 the nozzle in contact with the formulation causing the atomisation of the liquid to form a spray of electrically charged droplets for application to an eye.

30 This method thus requires the use of co-ordination of moving parts (the piston) and the triggering of the voltage.

One object of the present invention is to obviate the need for moving parts and to provide apparatus which is able to atomise a small quantity of liquid 35 such as a single drop of liquid using electrostatic

forces alone.

The invention therefore provides apparatus for dispensing an aerosol of electrostatically charged droplets comprising a housing having an open ended duct in which are located first electrode having an upper surface lying in a generally longitudinal plane of the duct, and a second electrode spaced from the first electrode, the apparatus further comprising means for delivering a metered quantity of liquid to the upper surface of the first electrode for atomisation and charging means for applying a higher potential to the second electrode with respect to the first electrode to effect atomisation.

A preferred embodiment of the present invention will now be described, by way of example only, and with reference to the accompanying drawings in which:-

Fig. 1 is a cross section of a side elevation of the atomising section of dispensing apparatus according to the present invention.

The dispensing apparatus of the present invention includes a housing (not shown) having an atomising section shown in Fig. 1. The atomising section includes a horizontally extending cylindrical duct 10 which is open at both ends through which air can flow. One end defines an air inlet 11 and the other defines or communicates with an inhalation port 12 suitable for oral inhalation.

Located within the cylindrical duct 10 is a first electrode 13, which is preferably mushroom shaped having an annular head 13a with a gently convexly curved upper surface 15. The first electrode is positioned so that the head 13a lies substantially in a longitudinal direction in the duct 10. The first

electrode 13 is preferably earthed via the stem 13b of the electrode 13 which protrudes from the duct 10.

Also located within the cylindrical duct 10 is a second electrode 14, which second electrode 14 is 5 connected to a charging circuit capable of applying a potential to the second electrode 14 greater than that of the first electrode 13 of 10 to 20kV. The second electrode 14 is preferably a single wire, the point of entry of which into the duct 14 is offset in a 10 longitudinal direction from the axis of the stem 13b of the first electrode 13. Typically the electrodes are 0.5 to 5cm apart at the closest point. The second electrode 14 may be completely enclosed in an 15 insulating material thereby mechanically shielding the electrode 14 from the patient and any objects inserted into the mouthpiece 12.

The housing further houses means (not shown) for delivering liquid to the first electrode 13, either directly to the upper rounded surface 15 or via a 20 channel 16 through the stem 13b of the mushroom. The delivery means include metering apparatus to meter a small quantity of the liquid, such as a single drop of 25 preferably between 20-50 $\mu$ l, or possibly more, of the liquid to be dispensed.

The liquid to be dispensed is preferably ethanol based and may be a water/ethanol mixture of up to 60% by volume concentrate of ethanol. However, other 30 liquids may be selected which are suitable for inhalation and which can be successfully atomised in stable electrohydrodynamic mode. Such liquids must preferably have a high resistivity and low surface tension and also preferably low permittivity. The preferred range of resistivity is between  $7.6 \times 10^3$  to 35  $1 \times 10^8 \Omega\text{m}$  and the preferred maximum surface tension is 0.04 N/m.

The housing further houses a charging circuit and power supply battery. The battery is electrically connected by means of appropriate wiring to the second electrode 14.

5 In use a metered quantity, such as a drop of liquid is delivered to the first electrode 13. Due to the low surface tension of the liquid it spreads out over the surface of the first electrode 13.

10 Gravitational forces cause a greater build up of liquid around the perimeter of the head 13a than elsewhere on the head. The charging circuit is energised to apply a DC voltage of 10 to 20kV to the second electrode 14. The resulting electric field at the edge of the first electrode 13 causes the liquid 15 to atomise at the periphery of the mushroom electrode 13 in the form of atomised droplets. The atomisation of the liquid takes place only on the edge of the head 13a and the strong ionic wind created by the end of the second electrode 14 forces the spray of highly 20 charged droplets produced during the electrostatic atomisation along the cylinder 10 at a low velocity to the mouthpiece 12 without any additional air flow. Once all the liquid has been atomised, the charging circuit is switched off.

25 Further means may be provided to modify the charge on the droplets, to reduce, enhance, neutralise or reverse the charge.

30 In alternative embodiments of the present invention the second electrode 14 may be provided in the form of a mesh located above the first electrode 13. Alternatively it could be in the form of a ring, an ellipse or a squashed ellipse with the wires 35 touching. The first electrode 13 may alternatively be T-shaped or Y-shaped in cross-section. The first electrode may also be made of or covered with a porous

material.

The potential applied to the second electrode 14 is preferably selected to minimise droplet deposition on the second electrode 14. However it is also 5 possible to include a means of providing additional air flow to help reduce this deposition.

A further embodiment of the invention can be used to atomise a continuous stream of liquid for use in a nebuliser. In this embodiment the delivery means 10 continuously supply liquid to the first electrode 13 to replace the atomised liquid while continually applying potential to the electrode 14.

15

20

25

30

35

CLAIMS:

1. Apparatus for dispensing an aerosol of electrostatically charged droplets comprising a  
5 housing having an open ended duct in which are located first electrode having an upper surface lying in a generally longitudinal plane of the duct, and a second electrode spaced from the first electrode, the apparatus further comprising means for delivering a  
10 metered quantity of liquid to the upper surface of the first electrode for atomisation and charging means for applying a higher potential to the second electrode with respect to the first electrode to effect atomisation.
- 15 2. Apparatus as claimed in claim 1 in which the potential difference between the electrodes is between 10 and 20kV.
- 20 3. Apparatus as claimed in claim 1 or claim 2 in which the first electrode is earthed.
- 25 4. Apparatus as claimed in any one of the preceding claims in which the second electrode is a single wire.
- 30 5. Apparatus as claimed in claim 4 in which the second electrode enters the duct at an entry point offset in a longitudinal direction with respect to an axis through the centre of the convexly curved annular surface of the first electrode.
- 35 6. Apparatus as claimed in any one of the preceding claims in which the second electrode is insulated.
7. Apparatus as claimed in any one of the preceding

- 8 -

claims in which the first electrode comprises a head, bearing the convexly curved structure and a stem projecting therefrom.

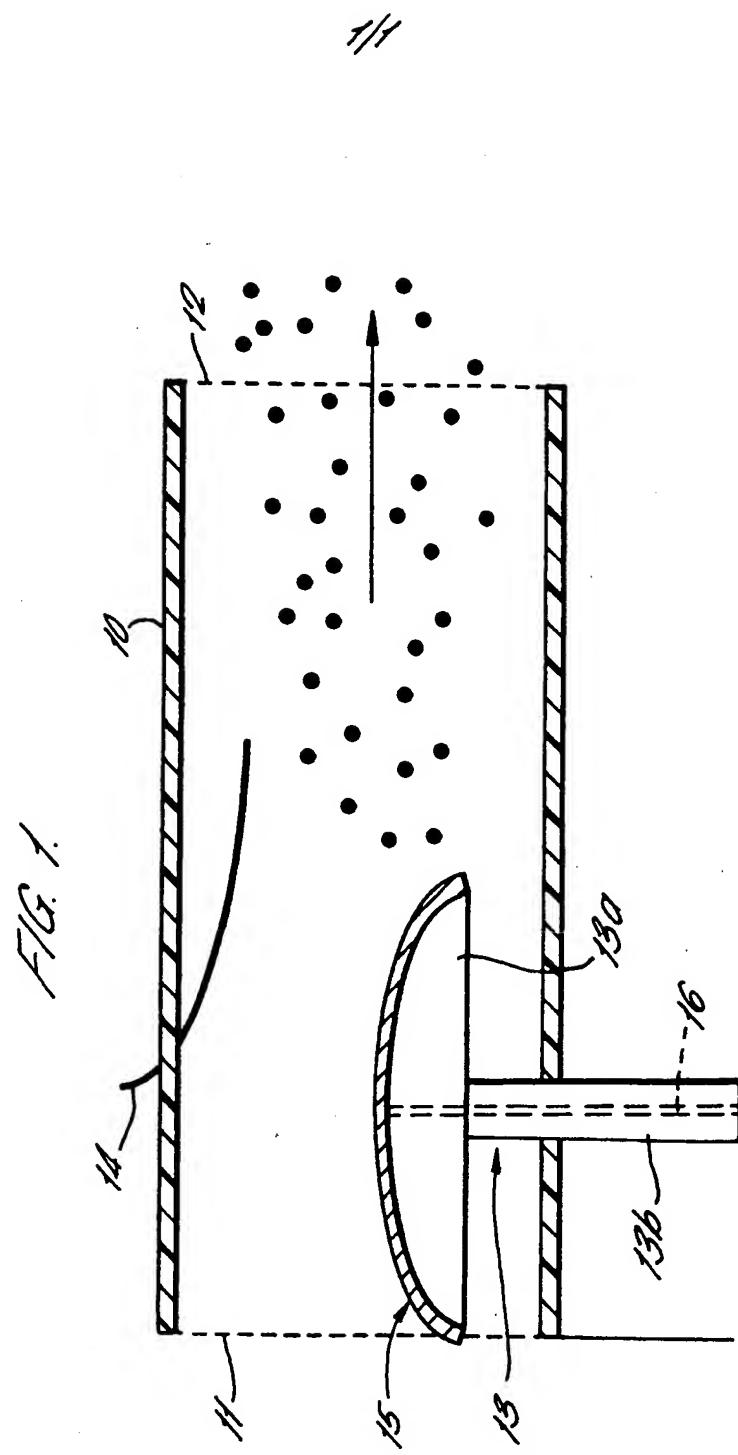
5 8. Apparatus as claimed in claim 7 in which the delivery means deliver liquid to the upper surface of the first electrode via a channel in the stem.

10 9. Apparatus as claimed in any one of the preceding claims in which the liquid is ethanol based.

15 10. Apparatus as claimed in any one of the preceding claims in which means are provided downstream of the first and second electrodes to modify the charge on the atomised droplets.

11. Apparatus as claimed in any one of the preceding claims in which the delivery means continuously deliver a metered quantity of liquid to the first 20 electrode for dispensing a continuous aerosol.

12. Apparatus substantially as hereinbefore described with reference to and as shown in the accompanying drawings.



# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/GB 98/03415

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61M15/00 B05B5/025

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61M B05B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 511 726 A (GREENSPAN BERNARD J ET AL) 30 April 1996 see column 3, line 37 - column 4, line 22; figure 1 ---	1,2,4
A	WO 94 14543 A (ELECTROSOLS LTD ;COFFEE RONALD ALAN (GB)) 7 July 1994 see claims; figures 1-4 ---	1,2
A	US 1 958 406 A (DARRAH) 15 May 1934 see page 1, line 24 - line 70; figure 1 ---	1,6
A	WO 96 40441 A (ICI PLC ;GREEN MICHAEL LESLIE (GB); NOAKES TIMOTHY JAMES (GB); PRE) 19 December 1996 see claims; figures ---	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 1999	10/05/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo rd, Fax: (+31-70) 340-3018	Authorized officer  Villeneuve, J-M

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Jonal Application No

PCT/GB 98/03415

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5511726	A 30-04-1996	US 5115971 A		26-05-1992
		AT 99564 T		15-01-1994
		AU 635902 B		08-04-1993
		AU 4302589 A		18-04-1990
		CA 1339281 A		12-08-1997
		DE 68912133 D		17-02-1994
		DE 68912133 T		28-04-1994
		EP 0435921 A		10-07-1991
		JP 4500926 T		20-02-1992
		PT 91786 A,B		30-03-1990
		WO 9003224 A		05-04-1990
WO 9414543	A 07-07-1994	AU 684735 B		08-01-1998
		AU 5709894 A		19-07-1994
		AU 6069998 A		11-06-1998
		CN 1090227 A		03-08-1994
		EP 0675764 A		11-10-1995
		JP 8504670 T		21-05-1996
		NZ 258988 A		26-01-1998
		ZA 9309614 A		31-01-1995
US 1958406	A 15-05-1934	NONE		
WO 9640441	A 19-12-1996	AU 3525995 A		26-04-1996
		AU 5829496 A		30-12-1996
		BR 9509252 A		21-10-1997
		CA 2200181 A		11-04-1996
		CA 2222519 A		19-12-1996
		CN 1159773 A		17-09-1997
		CN 1192168 A		02-09-1998
		CZ 9701003 A		13-08-1997
		EP 0776253 A		04-06-1997
		EP 0837736 A		29-04-1998
		WO 9610459 A		11-04-1996
		HU 76948 A		28-01-1998
		JP 10506324 T		23-06-1998
		PL 319482 A		04-08-1997
		SK 42197 A		10-09-1997